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BAKER & DANIELS LLP
111 E. WAYNE STREET
SUITE 800
FORT WAYNE, IN 46802

EXAMINER
SAJJADI, FEREYDOUN GHOTB

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,539	ONO ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3 and 5-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3 and 5-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 April 2007* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Applicants' response of April 30, 2007, to the non-final action dated November 1, 2006 has been entered. Claims 2, 3 and 5-13 are pending in the application. Claims 2, 3 and 5-9 have been amended, claim 1 has been cancelled and claims 10-13 are newly added. Claims 2, 3 and 5-13 are currently under examination.

Response to Objections to the Specification/Abstract

Applicants have provided a new Abstract of the disclosure on a separate sheet, apart from any other text, in accordance with 37 CFR 1.52(b)(4). Thus, the objection to the Abstract is hereby withdrawn.

The objection to the Figures referred to in the text of the disclosure is maintained, because while Applicants have provided a copy of Figures 1-6, the specification is still devoid of a brief description of the drawing figure(s).

Response to Nucleotide Sequence Disclosures 37CFR §1.821-1.825

In view of Applicants' amendments to the specification, to refer to the primer sequences by appropriate SEQ ID NOS, and the newly submitted sequence listing in compliance with 37 CFR 1.821-1.825, the previous objection is hereby withdrawn.

Response & New Claim Objections

Claims 1-9 were previously objected to in the office action dated November 1, 2006, as lacking the articles "A" and "The" at the beginning of the claims. Applicants have amended the claims to recite the missing articles. Thus, the previous objection is hereby withdrawn.

Claims 2-9 are newly objected to because of the following informalities: Claims 2-9 constitute improper dependent claims, as they do not refer back, or depend from a preceding claim. Appropriate correction and claim renumbering is required.

Response and New Claim Rejections - 35 USC § 112- Second Paragraph

Applicants' claim amendments have necessitated the following new grounds of rejection. Claims 1-9 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Applicants' cancellation of claims 1 and 4 renders their rejections moot. The ground of rejection set forth on pp. 4-5 is maintained for claims 2, 3 and 5-9 and is applied to newly added claims 10-13 for reasons of record and the following commentary.

Applicants state that the amended claims obviate the indefiniteness rejections. Such is not found persuasive, because the amendments only partly address the previous grounds for rejection. Newly added base claim 10 recites language similar to that of cancelled claim 1, and hence is newly rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: introduction of the transgene by microinjection into the fertilized embryo pronucleus and the implantation of said embryo into a pseudopregnant mouse; or the introduction of the transgene into mouse ES cells, and following homologous recombination in the ES cell genome, the ES cells are transferred by microinjection into the blastocyst of a fertilized embryo, said blastocyst is subsequently implanted into a pseudopregnant mouse.

Claim 10 is further unclear in reciting the limitation: "wherein said introduced transgene expresses said extracellular domain and said fragment"; because it is not clear how transgene expression may take place in the absence of an operably linked promoter.

Claims 2, 3, 5-9 and 11-13 depend from claim 10, and are therefore included in the rejection.

Response & New Claim Rejections - 35 USC § 112 – Written Description

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 1-9 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Applicants' cancellation of claims 1 and 4 renders their rejections moot. The ground of rejection set forth on pp. 5-7 is maintained for claims 2, 3 and 5-9 and is further applied to newly added claims 10-13 for reasons of record.

Applicants disagree with the rejection, arguing that the polypeptide sequence of nectin-1 is remarkably well conserved between porcine and bovine species of mammals, which provides a reasonable basis for assuming a significant structural and functional identity between the two species; that the names HveC and nectin-1 refer to the same polypeptide and Example 2 of the instant specification refers to resistance to the virus PRV of transgenic mice, into which has been introduced a coding transgene for a chimeric protein consisting of the extracellular domain of the porcine receptor HveC (and not the murine receptor HVEM) and crystallizable fragment Fc of the human immunoglobulin IgG-1.

Applicants' arguments have been fully considered, but are not found persuasive. The previous office action stated that he specification only discloses the chimeric proteins containing the extracellular domain of Hvem (specifically, the mouse and porcine HveC) fused to the Fc portion of the human immunoglobulin IgG-1, introduced into the fertilized mouse embryo pronuclei (pp. 11 and 16), but does not describe the structure or functional nature of any chimeric proteins containing parts or sub-parts of nectin-1 or HveC from numerous species of animals that would include peptides yet to be discovered.

It should be noted that the instant claims are not limited to the porcine and bovine species, but rather, any species of mammal. Moreover, the claims encompass any parts of the extracellular domain of nectin-1, that would further retain an ability to confer resistance to an infection by any alphaherpes virus. However, the instant specification is silent on which parts of nectin-1 from any species of mammals would retain such an activity, thus possession of the numerous species has not been demonstrated at the time of the invention. Thus it is maintained that the written description requirement is not satisfied for the claimed genus

Response & New Claim Rejections - 35 USC § 112-Lack of Enablement

Applicants' claim amendments have necessitated the following new grounds of rejection. Claims 1-9 stand rejected under 35 U.S.C.§112, first paragraph, as failing to comply with the enablement requirement. Applicants' cancellation of claims 1 and 4 renders their rejections moot. The ground of rejection set forth on pp. 8-11 is maintained for claims 2, 3 and 5-9 and is further applied to newly added claims 10-13 for reasons of record.

Applicants disagree with the rejection, arguing that the invention of claims is sufficiently taught by the instant specification, citing Examples 1-4. Applicants further state that the Examiner submits on page 12 of the office action that claims 1-5 are enabled for transgenic mice. Applicants' arguments have been fully considered, but are not found persuasive.

It should be noted that the Examiner has been quoted out of context by Applicants in reference to page 12 of the previous office action. Page 12 addresses the rejection of claims 1-5 under 35 USC 103(a) and states that the rejection over the prior art is applicable to the extent that the claims are enabled for a transgenic mice encoding a chimeric HveC/Fc IgG fusion protein. However, the instant claims are not limited to mice or the intact HveC extracellular domain in a chimeric HveC/Fc IgG fusion protein.

The previous office action stated the instant specification is non-enabling based on two separate issues, that the specification does not provide an enabling disclosure for the production of numerous transgenic non-human mammals or the generation of said transgenic mammals by homologous recombination; and that the specification does not provide an enabling disclosure for the production of transgenic mammals expressing fusion proteins of nectin-1 or its parts.

As previously indicated, the specification states that infection mediator abilities of HveC in relation to the entry of the targeted virus, so as to ultimately inhibit the entry of this virus into the cell and favor its elimination, is by a process which is still to be determined (p. 7). The specification is silent however, on the introduction of any transgenes by homologous recombination into a targeted chromosomal location. Tables 1-4 disclose data from the various transgenic lines, showing different concentrations of mouse HVEM-Ig in the serum of the mice, with 3 of the 4 lines with the highest HVEM-Ig concentration showing resistance to HSV-1 intravenous virus infection (p. 13). However, the mice were not protected against infection by PRV virus (p. 14), thus suggesting the presence of tropism for different alphaherpesviruses. Table 6 discloses results from transgenic mice expressing a porcine HVEM-Ig transgene, wherein viral challenge by intra-peritoneal injections of PRV virus resulted in the survival of the mice (p. 17), but survival was reduced to 70% when virus was introduced intranasally (Table 7 and pp. 17-18). The specification is absent any data from the intravenous administration of PRV to these mice. Therefore, the data suggest that the route of infection likely plays a role in the degree of resistance to viral infection, though the mechanism of said resistance remains

unknown. Further, resistance to infection appears to be dependent on both the type of HveC receptor and the particular alphaherpesvirus. As the specification fails to disclose either a transgenic bovine or a transgenic porcine expressing an HveC fusion protein, any resistance of these transgenic animals to PRV or BHV-1 virus infections remains unknown and would have to be determined by further experimentation.

Applicants argue that it is irrelevant that the *in vivo* experiments were only carried out in a mouse model that is easier to use and that experiments have shown there is indeed little difference between mouse and porcine species. Applicants further argue that the publication of Mullins et al. does not reflect the state of the art at the time of filing of the invention. Such is not found persuasive, because the fact that a given construct may react differently from one species to another remains unchanged, as the structural and functional particulars of a species has not changed and the differences among the different species of mammals remains the same. Furthermore, the differences between mice and any other species of mammal as instantly claimed are significant, especially with respect to embryonal stem cell technology and the application of homologous recombination. In response to Applicants' arguments against the Machaty reference, that by generating several lines, it can be shown without undue experimentation whether there is a correlation between the expression of a chimeric protein and the effect obtained, it should be noted that the reference of Machaty et al. serves to show the unpredictability in generating transgenic animals by pronuclear microinjection of transgenes and the generation of multiple founder lines does not obviate such unpredictability. Further, Machaty et al. state that the generation of transgenic animals by homologous recombination of transgenes, necessitates the use of ES cells, that while proven in mice, have not been developed in other animals, such as pigs (Machaty et al., second column, p 22). Applicants have failed to address issues raised either with respect to ES cells in any mammal, or the presence of tropism for different alphaherpesviruses and the particular nectin-1 receptor utlilized. Applicants have further failed to address issues relating to fusion proteins comprising the parts of the extracellular domain of nectin-1.

Applicants argue that transgenic pigs have now been obtained that express the extracellular domain of nectin-1 fused with the Fc fragment of human IgG. However, the data provided fails to obviate the grounds for rejection, as the transgenic pigs were not produced by a

transgene encoding any parts of any nectin-1, or by homologous recombination; and were not shown to have been rendered resistant to an infection by any alphaherpes virus, as only *in vitro* antibody results have been presented.

Therefore, the ground of rejection is maintained for reasons of record and the foregoing discussion.

Response & New Claim Rejections - 35 USC § 103

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 1-5 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Fiume et al. (U.S. Patent No.: 6,469,155, filed Nov. 9, 1999), in view of Bujard et al. (US. Patent No.: 5,866,755, Feb. 2, 1999). Applicants' cancellation of claims 1 and 4 renders their rejections moot. The ground of rejection set forth on pp. 12-13 is maintained for claims 2, 3 and 5 and is further applied to newly added claims 10-12 for reasons of record.

Applicants disagree with the rejection, stating that the claimed invention is unobvious over the prior art, and argue that the specific functional receptor nectin-1, which is present on the surface of many types of cells, is used outside its physiological context, and that the claimed invention is further patentable in reciting an extracellular domain that is truncated (that is, "a part thereof") from the form normally present. Applicants' arguments have been fully considered, but are not found persuasive.

Fiume et al. describe various fusion proteins between various segments of HIgR (herpesvirus immunoglobulin-like receptor) and the Fc portion of human IgG1 (Abstract and column 4). Specifically described are sVCC(PVRα)-Fc containing the soluble V domains of HIgR (column 4 and Example 4), in addition to the discovery in the prior art that a soluble form of HveC containing the entire ectodomain is capable of such binding (column 17). Fiume et al. further state that an object of their invention is to provide cells that are resistant to infection by HSV-1, HSV-2 and BHV-1 (column 1). Fiume et al. state that an embodiment of their invention is the construction of transgenic mice expressing the alphaherpesvirus receptors that mediate HSV and BHV-1 entry, from transgenes to produce a mouse model system for the viral

infections (column 3). Thus, utilizing domains or parts of a nectin-1 outside its physiological context, and meeting the limitation of the instant claims.

Applicants cite the article by Ono, et al. to show that researchers have attempted to produce lines of animals resistant to infection by alphaherpesviruses as early as the late 1980s, but that these attempts were unsuccessful. In response, Applicants should note that the prior art rejection has been applied only to the extent that the claims read on transgenic mice rendered resistant to an infection by an alphaherpesvirus, said mice containing a transgene encoding a chimeric HveC/Fc IgG fusion protein, and a process of producing said mice. The object of the Fiume patent is to utilize HIGR and related domains which bind the glycoprotein D of herpes simplex virus in preventing infection by said virus (Title and Abstract). Further, the combined teachings of Ono et al. and Bujard et al. render obvious the application of their invention to transgenic mice. Thus, Applicants' statement that the Fiume patent does not teach or suggest the skilled artisan to produce a mammal rendered resistant to alphaherpesvirus infection is contrary to the teachings of Fiume et al.

Therefore the rejection is maintained for claims 2, 3 and 5 and is further applied to newly added claims 10-12 for reasons of record and the foregoing discussion.

Conclusion

Claims 2, 3 and 5-13 are not allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00-4:00 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on **(571) 272-0739**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

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Fereydoun G. Sajjadi, Ph.D.
Examiner, USPTO, AU 1633

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633